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(54) Title: *CIS*-Δ^4 ANALOGS OF PROSTAGLANDINS AS OCULAR HYPOTENSIVES

(57) Abstract

Cis-Δ^4 analogs of prostaglandins and methods of their use in treating glaucoma and ocular hypertension are disclosed.

CIS-Δ^4 ANALOGS OF PROSTAGLANDINS AS OCULAR HYPOTENSIVES

Background of the Invention

The present invention relates to novel compounds for the treatment of glaucoma and ocular hypertension. In particular, the present invention relates to the use of certain *cis*-Δ^4 analogs of D and F series prostaglandins to treat glaucoma and ocular hypertension.

Glaucoma is a progressive disease which leads to optic nerve damage, and, ultimately, total loss of vision. The causes of this disease have been the subject of extensive studies for many years, but are still not fully understood. The principal symptom of and/or risk factor for the disease is elevated intraocular pressure or ocular hypertension due to excess aqueous humor in the anterior chamber of the eye.

The causes of aqueous humor accumulation in the anterior chamber are not fully understood. It is known that elevated intraocular pressure ("IOP") can be at least partially controlled by administering drugs which either reduce the production of aqueous humor within the eye, such as beta-blockers and carbonic anhydrase inhibitors, or increase the flow of aqueous humor out of the eye, such as miotics and sympathomimetics.

Most types of drugs conventionally used to treat glaucoma have potentially serious side effects. Miotics such as pilocarpine can cause blurring of vision and other visual side effects, which may lead either to decreased patient compliance or to termination of therapy. Systemically administered carbonic anhydrase inhibitors can also cause serious side effects, such as nausea, dyspepsia, fatigue, and metabolic acidosis, which side effects can affect patient compliance and/or necessitate the termination of treatment. Beta-blockers have increasingly become associated with serious pulmonary side effects

attributable to their effects on beta-2 receptors in pulmonary tissue. Sympathomimetics may cause tachycardia, arrhythmia and hypertension. Recently, certain prostaglandins and prostaglandin derivatives have been described in the art as being useful in reducing intraocular pressure. Typically, however, prostaglandin therapy for the treatment of

5 elevated intraocular pressure is attended by undesirable side-effects, such as irritation and hyperemia of varying severity and duration. There is therefore a continuing need for therapies which control elevated intraocular pressure associated with glaucoma without the degree of undesirable side-effects attendant to most conventional therapies.

10 Prostaglandins are metabolite derivatives of arachidonic acid. Arachidonic acid in the body is converted to prostaglandin G_2, which is subsequently converted to prostaglandin H_2. Other naturally occurring prostaglandins are derivatives of prostaglandin H_2. A number of different types of prostaglandins have been discovered including A, B, D, E, F,G,I and J-Series prostaglandins (EP 0 561 073 A1). Of interest in

15 the present invention are compounds which are believed to exhibit IOP lowering mechanisms similar to those exhibited by PGD_2 (a D-series prostaglandin of formula I) and $PGF_{2\alpha}$ (an F-series prostaglandin of formula II):

20
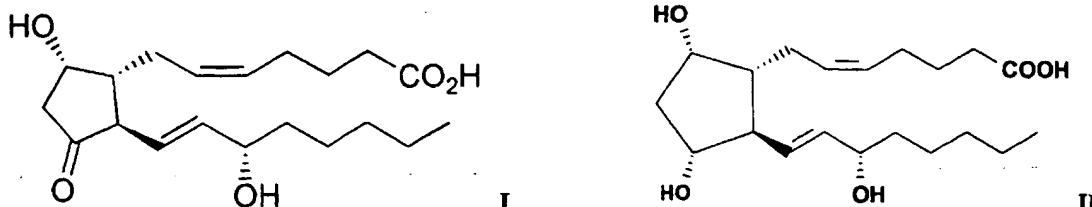
The relationship between PGD_2 receptor activation and IOP lowering effects is not well understood. Various publications have reported that PGD_2 receptor activation leads

25 to second messenger activation and in particular, to the stimulation of adenylate cyclase and resultant increases in cAMP levels (Thierauch, *Prostaglandins and their Receptors: II. Receptor Structure and Signal Transduction*, Journal of Hypertension, volume 12, pages 1-5 (1994). Regardless of the mechanism, PGD_2 has been shown to lower IOP (Nakajima,

Effects of Prostaglandin D₂ and its analogue, BW245C, on Intraocular Pressure in Humans, Graefe's Archive Ophthalmology, volume 229, pages 411-413 (1991)). Thus, it has been of interest in the ophthalmic field to develop synthetic PGD$_2$ analogs with IOP lowering efficacy.

Synthetic PGD$_2$-type analogs have been pursued in the art (Graefe's Archive Ophthalmology, volume 229, pages 411-413 (1991)). Though PGD$_2$-type molecules lower IOP, these types of molecules have also been associated with undesirable side effects resulting from topical ophthalmic dosing. Such effects have included an initial increase in IOP, conjuctival hyperemia, increases in microvascular permeability, and increases in eosinophile infiltration (Alm, *The Potential of Prostaglandin Derivatives in Glaucoma Therapy*, Current Opinion in Ophthalmology, volume 4, No. 11, pages 44-50 (1993)).

Similarly, the relationship of PGF$_{2\alpha}$ receptor activation and IOP lowering effects is not well understood. It is believed that PGF$_{2\alpha}$ receptor activation leads to increased outflow of aqueous humor. Regardless of the mechanism, PGF$_{2\alpha}$ and certain of its analogs have been shown to lower IOP (Giuffre, *The Effects of Prostaglandin F$_{2\alpha}$ the Human Eye*, Graefe's Archive Ophthalmology, volume 222, pages 139-141 (1985); and Kerstetter et al., *Prostaglandin F$_{2\alpha}$-1-Isopropylester Lowers Intraocular Pressure Without Decreasing Aqueous Humor Flow*, American Journal of Ophthalmology, volume 105, pages 30-34 (1988)). Thus, it has been of interest in the field to develop synthetic PGF$_{2\alpha}$ analogs with IOP lowering efficacy.

Synthetic PGF$_{2\alpha}$-type analogs have been pursued in the art (Graefe's Archive Ophthalmology, volume 229, pages 411-413 (1991)). Though PGF$_{2\alpha}$-type molecules lower IOP, a number of these types of molecules have also been associated with undesirable side effects resulting from topical ophthalmic dosing. Such effects include an initial increase in IOP, breakdown of the blood aqueous barrier and conjunctival

hyperemia (Alm, *The Potential of Prostaglandin Derivatives in Glaucoma Therapy*, Current Opinion in Ophthalmology, volume 4, No. 11, pages 44-50 (1993)).

Based on the foregoing, a need exists for the development of molecules that may activate the PGD_2 and/or $PGF_{2\alpha}$ receptors, yielding a more efficacious lowering of IOP, while exhibiting fewer or reduced side effects.

An agent which exhibits the same or improved efficacy, but with reduced side effects when compared to other agents, is said to have an improved therapeutic profile. It is an object of this invention to provide a class of IOP lowering agents with an improved therapeutic profile over their $PGF_{2\alpha}$ and PGD_2 counterparts, and methods of their use. It has now unexpectedly been discovered that the presently claimed *cis*-Δ^4 analogs of $PGF_{2\alpha}$ and PGD_2 meet this objective. Certain *cis*-Δ^4 analogs of $PGF_{2\alpha}$ (Nedy and Johnson, J. Org. Chem., 45:6, 1121 (1980); Bowler *et. al.* Prostaglandins, 17:6, 789 (1979); DE 2,716,972; DE 2,637,384; DE 2,623,139; US 3,954,835) and PGD_2 (EPO 299,914 B1) are known in the art. The metabolic profiles of *cis*-Δ^4 $PGF_{2\alpha}$ and (15S)-15-methyl- *cis*-Δ^4 $PGF_{2\alpha}$ relative to the corresponding *cis*- Δ^5 isomers have also been discussed in the art (Green *et. al.*, Eur. J. Biochem., 62, 527 (1976); Green, Prostaglandins, 15:5, 813 (1978); Hansson, Prostaglandins, 18:5, 745 (1979); Tarpley and Sun, J. Med. Chem., 21:3, 288 (1978)). However, the surprisingly enhanced therapeutic profiles of such compounds and the novel compounds of the present invention in the treatment of glaucoma are neither disclosed nor suggested in that art.

Summary of the Invention

The present invention is directed to compositions and methods of their use in treating IOP and ocular hypertension. In particular, the present invention provides certain classes of *cis*-Δ^4 prostaglandin analogs, and methods of their use in treating glaucoma and ocular hypertension. As previously stated, the mechanism of action by which PGD_2 and $PGF_{2\alpha}$ type prostaglandins lower IOP is not well understood. Nevertheless, without being

bound by any theories, the inventors postulate that the compounds of the present

invention, with a *cis* double bond between carbons 4 and 5 in the alpha (α) chain, are less

susceptible to metabolic degradation than are their non-*cis*-Δ^4 counterparts, and therefore

enjoy a longer *in vivo* half-life than the non- *cis*-Δ^4 compounds. A longer *in vivo* half life

5   should enable relatively lower dosing and a reduction in side effects.

Detailed Description of the Invention

10   It has unexpectedly been found that *cis*-Δ^4 analogs of the present invention exhibit

an improved therapeutic profile in the treatment of glaucoma and ocular hypertension

when compared to natural prostaglandins and many of their known analogs. The *cis*-Δ^4

analogs of the present invention are heptenoic acid derivatives having the following

formula **III**:

15

III
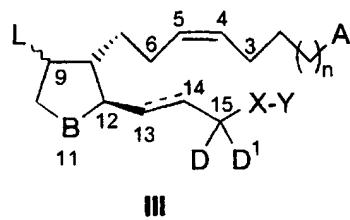
wherein:

20   A = CO_2R, $CONR^1R^2$, CH_2OR^3, or $CH_2NR^4R^5$; where R = H or cationic salt moiety, or

CO_2R = pharmaceutically acceptable ester moiety; R^1, R^2 = same or different = H or alkyl;

R^3 = H, acyl, or alkyl; R^4, R^5 = same or different = H, acyl, or alkyl, with the proviso that

if one of R^4, R^5 = acyl, then the other = H or alkyl;

25   n = 0 or 2;

L = OR^6 in the α configuration, where R^6 = H, alkyl, or acyl; or L = halo in either

configuration;
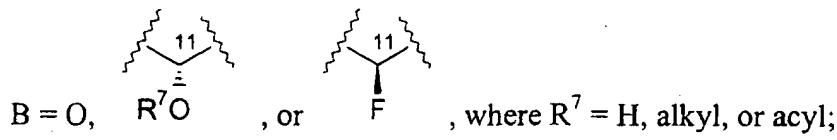
-5-

$B = O,$ [structure with label 11, R^7O], or [structure with label 11, F], where R^7 = H, alkyl, or acyl;

---- = single or *trans* double bond;

D, D^1, taken together = OCH_2CH_2O; or D, D^1 = different = H and OR^8, where R^8 = H, alkyl, or acyl; or D = fluorine in the α configuration, and D^1 = H in the β configuration;

X = $(CH_2)_m$ or $(CH_2)_mO$, where m = 1-6; and

Y = a phenyl ring optionally substituted with alkyl, halo, trihalomethyl, alkoxy, acyl, acyloxy, amino, alkylamino, acylamino, or hydroxy; or

X-Y = $(CH_2)_pY^1$; where p = 0-6; and

Y^1 = [structure with W and Z substituent] or [structure with W and Z substituent]
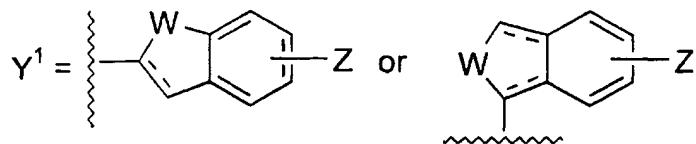
wherein:

W = CH_2, O, $S(O)_q$, NR^9, CH_2CH_2, CH=CH, CH_2O, $CH_2S(O)_q$, CH=N, or CH_2NR^9; where q = 0-2, and R^9 = H, alkyl, or acyl;

Z = H, alkyl, alkoxy, acyl, acyloxy, halo, trihalomethyl, amino, alkylamino, acylamino, or hydroxy; and

---- = single or double bond;

or X-Y = cyclohexyl;

with the proviso that the following compounds of formula **III** be excluded: those wherein:

L = OR^6 in the α configuration, where R^6 is as defined above;

B = (structure) , where R^7 is as defined above;
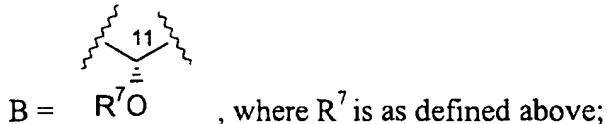
--- = *trans* double bond;

D, D^1 = different = H and OR^8, where R^8 is as defined above;

X = CH_2CH_2 or CH_2O; and

Y = a phenyl ring, optionally substituted with halo.

For purposes of the foregoing and following definitions, the term "pharmaceutically acceptable ester" means any ester that would be suitable for therapeutic administration to a patient by any conventional means without significant deleterious health consequences; and "ophthalmically acceptable ester" means any pharmaceutically acceptable ester that would be suitable for ophthalmic application, i.e. non-toxic and non-irritating. Preferred are alkyl esters. Most preferred are C_2-C_4 alkyl esters, and especially isopropyl esters. For compounds of formula **III** where L = halo, preferred is chlorine in the β configuration.

Preferred for use in the methods and compositions of the present invention are those compounds of formula **III** above, wherein:

A = CO_2R, where R = H; or CO_2R = pharmaceutically acceptable ester moiety selected from the group consisting of ophthalmically acceptable ester moieties, where R = alkyl;

$n = 0$;

$L = OH$ in the α configuration;

$B = O$,   [structure with label 11, HO], or [structure with label 11, F] ;
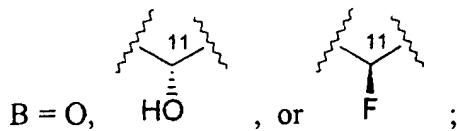
5

D, D^1, taken together $= OCH_2CH_2O$; or $D = OH$ in the α configuration, and $D^1 = H$ in the β configuration; or $D =$ fluorine in the α configuration, and $D^1 = H$ in the β configuration;

$X = CH_2CH_2$ or CH_2O; and

10

$Y =$ phenyl, optionally substituted with halo or trihalomethyl; or

$X-Y =$

[indane structure] ;
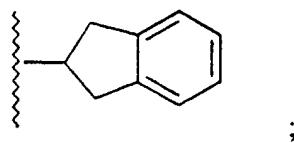
15

with the proviso that the following compounds of formula **III** be excluded, wherein:

$A = CO_2R$, where $R = H$ or alkyl;

20    $n = 0$;

$L = OH$ in the α configuration;

$B =$ [structure with label 11, HO] ;
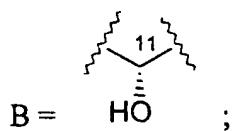
25

--- = *trans* double bond;

D = OH in the α configuration, and D^1 = H in the β configuration;

X = CH_2CH_2 or CH_2O; and

Y = a phenyl ring, optionally substituted with halo.

Especially preferred are the following compounds:

| Compound Number	Compound Name	Compound Structure
IV	(4Z,13E)-(9S,11R,15R)-16-(3-Trifluoromethylphenoxy)-9,11,15-trihydroxy-17,18,19,20-tetranor-4,13-prostadienoic acid isopropyl ester	
V	(4Z,13E)-(9S,11R,15S)-15-(2-Indanyl)-9,11,15-trihydroxy-16,17,18,19,20-pentanor-4,13-prostadienoic acid isopropyl ester	
VI	(4Z,13E)-(9S,11R)-16-(3-Chlorophenoxy)-9,11-dihydroxy-15-(1,3-dioxolan-2-yl)-17,18,19,20-tetranor-4,13-prostadienoic acid isopropyl ester	
VII	(4Z,13E)-(9S,11S,15R)-9,15-Dihydroxy-11-fluoro-16-[(3-trifluoromethyl)phenoxy]-17,18,19,20-tetranor-4,13-prostadienoic acid isopropyl ester	
VIII	Isopropyl [2R(1E,3R),3S(4Z),4R]-7-[Tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-4-hydroxy-3-furanyl]-4-heptenoate	
IX	(4Z)-(9S,11R,15R)-16-(3-Chlorophenoxy)-9,11-dihydroxy-15-fluoro-17,18,19,20-tetranor-4-prostenoic acid isopropyl ester	

Included within the scope of the present invention are the individual enantiomers of the title compounds, as well as their racemic and non-racemic mixtures. The individual enantiomers can be enantioselectively synthesized from the appropriate enantiomerically pure or enriched starting material by means such as those described below. Alternatively,

5   they may be enantioselectively synthesized from racemic/non-racemic or achiral starting materials. (*Asymmetric Synthesis* by J. D. Morrison and J. W. Scott, Eds., Academic Press Publishers: New York, 1983-1985 (five volumes) and *Principles of Asymmetric Synthesis* by R.E. Gawley and J. Aube, Eds., Elsevier Publishers: Amsterdam, 1996). They may also be isolated from racemic and non-racemic mixtures by a number of known methods,

10   e.g. by purification of a sample by chiral HPLC (*A Practical Guide to Chiral Separations by HPLC*, G. Subramanian, Ed., VCH Publishers: New York, 1994; *Chiral Separations* by HPLC, A.M. Krstulovic, Ed., Ellis Horwood Ltd. Publishers, 1989), or by enantioselective hydrolysis of a carboxylic acid ester sample by an enzyme (Ohno, M.; Otsuka, M. Organic Reactions, volume 37, page 1 (1989)). Those skilled in the art will appreciate that racemic

15   and non-racemic mixtures may be obtained by several means, including without limitation, nonenantioselective synthesis, partial resolution or even mixing samples having different enantiomeric ratios.

Believed to be novel are compounds of formula **III** which contain a bicyclic

20   aromatic group on the terminus of the ω chain, *i.e.*, those wherein:

A = CO_2R, $CONR^1R^2$, CH_2OR^3, or $CH_2NR^4R^5$; where R = H or cationic salt moiety, or CO_2R forms a pharmaceutically acceptable ester moiety; R^1, R^2 = same or different = H or alkyl; R^3 = H, acyl, or alkyl; R^4, R^5 = same or different = H, acyl, or alkyl, with the

25   proviso that if one of R^4, R^5 = acyl, then the other = H or alkyl;

n = 0 or 2;

L = OR^6 in the α configuration, where R^6 = H, alkyl, or acyl;

30

B = O,   R^{7}O   , or   F   , where R^7 = H, alkyl, acyl;
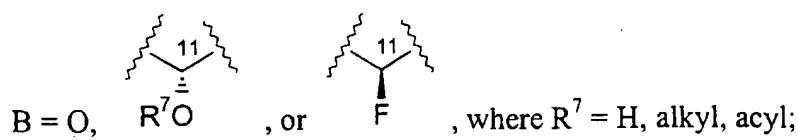
---- = single or *trans* double bond;

D, D^1, taken together = OCH$_2$CH$_2$O; or D, D^1 = different = H and OR^8, where R^8 = H,

alkyl, acyl; or D = fluorine in the α configuration, and D^1 = H in the β configuration;

X-Y = (CH$_2$)$_p$Y^1; where p = 0-6; and
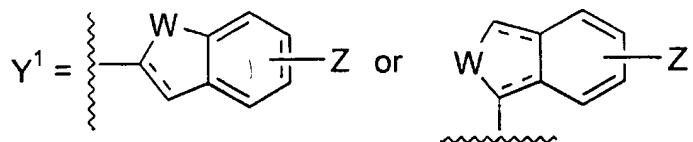
Y^1 = or

wherein:

W = CH$_2$, O, S(O)$_q$, NR^9, CH$_2$CH$_2$, CH=CH, CH$_2$O, CH$_2$S(O)$_q$, CH=N, or

CH$_2$NR^9; where q = 0-2, and R^9 = H, alkyl, or acyl;

Z = H, alkyl, alkoxy, acyl, acyloxy, halo, trihalomethyl, amino, alkylamino,

acylamino, or hydroxy; and

---- = single or double bond.

Other related compounds within the scope of the present invention are known and

their syntheses are either described in the literature or can be achieved by methods similar

to those described in the literature or otherwise known to those of skill in the art. . See, for

example, J. Org. Chem., 45:6, 1121 (1980); Prostaglandins, 17(6):789 (1979); Eur. J.

Biochem., 62:527 (1976); DE 2,826,462; DE 2,716,972; DE 2,623,139; EPO 299914 B1.

The contents of these references are by this reference incorporated herein in their entirety.

In the foregoing illustrations, as well as those provided hereinafter, wavy line attachments indicate either the alpha (α) or beta (β) configuration. The carbon numbering is as indicated in structural formula **III** (even when n = 2). A hatched line, as used e.g. at carbon 9, indicates the α configuration. A solid triangular line, as used e.g. at carbon 12, indicates the β configuration. Dashed lines on bonds, e.g. between carbons 13 and 14, indicate a single or double bond. Two solid lines between carbons indicate a double bond of the specified configuration.

In the following Examples 1-6, the following standard abbreviations are used: g = grams (mg = milligrams); mol = moles (mmol = millimoles); mL = milliliters; mm Hg = millimeters of mercury; mp = melting point; bp = boiling point; h = hours; and min = minutes. In addition, "NMR" refers to nuclear magnetic resonance spectroscopy and "MS" refers to mass spectrometry.

EXAMPLE 1:

Synthesis of IV
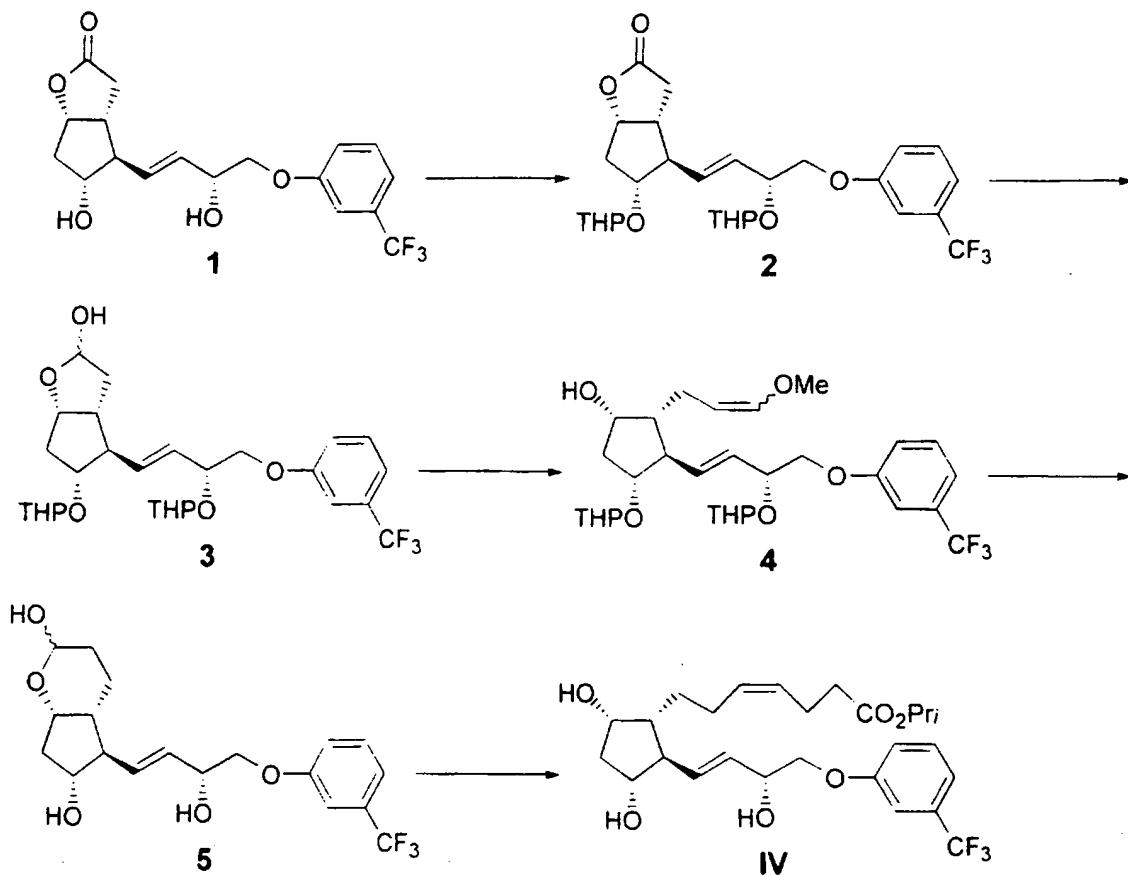
(4Z,13E)-(9S,11R,15R)-16-(3-Trifluoromethylphenoxy)-9,11,15-trihydroxy-17,18,19,20-tetranor-4,13-prostadienoic acid isopropyl ester **(IV)**

Reaction of diol **1** (for preparation, see U.S. Patent Number 4,321,275, which is incorporated by this reference) with 3,4-dihydro-2H-pyran in CH_2Cl_2 at 0 °C in the presence of p-toluenesulfonic acid (TsOH) affords THP ether **2**, which is reduced with diisobutylaluminum hydride (DIBAL-H) in toluene at -78 °C to afford lactol **3**. Wittig reaction of **3** with $Ph_3P^+CH_2OCH_3$ Cl⁻ in THF at 0 °C in the presence of potassium t-butoxide (KOBu^t) provides enol ether **4**, which is hydrolyzed with TsOH in THF/water to yield lactol **5**. Wittig reaction of **5** with $Ph_3P^+(CH_2)_3CO_2H$ Br⁻ in THF at 0 °C in the presence of KOBu^t, followed by alkylation of the product carboxylic acid with isopropyl iodide in acetone in the presence of DBU, yields **IV** after purification via silica gel chromatography.

EXAMPLE 2:

### Synthesis of V
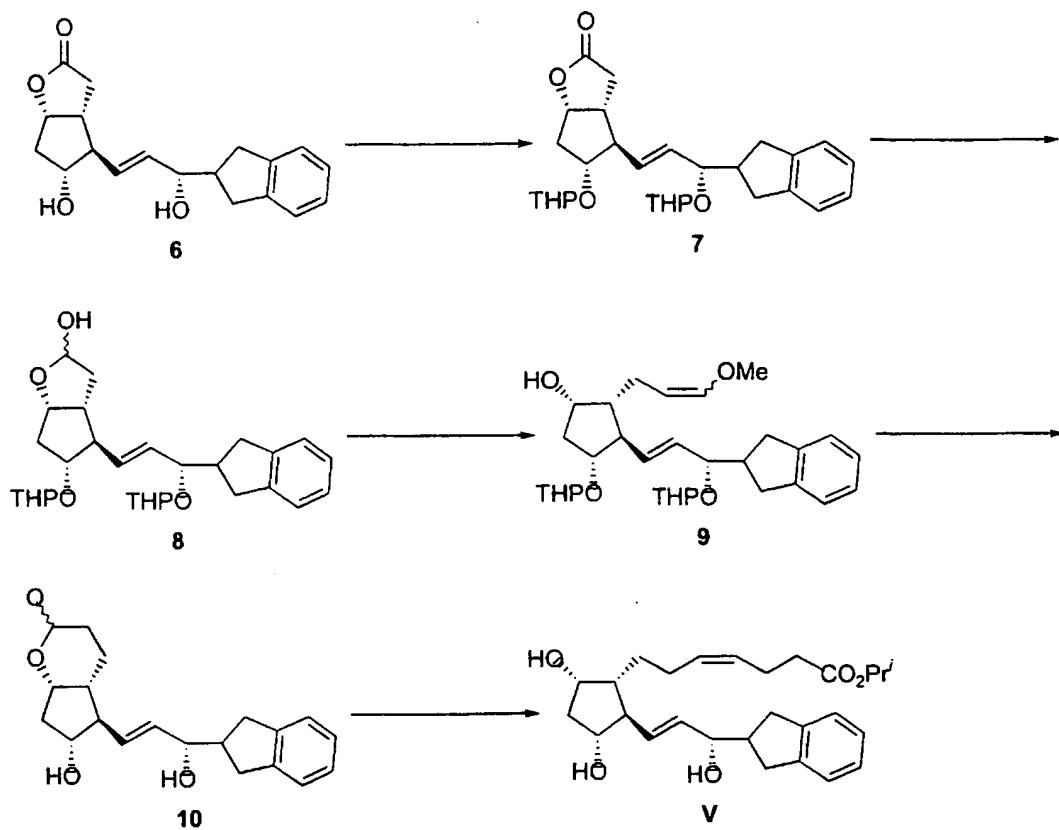
6

7

8

9

10

V

(4Z,13E)-(9S,11R,15S)-15-(2-Indanyl)-9,11,15-trihydroxy-16,17,18,19,20-pentanor-4,13-
prostadienoic acid isopropyl ester (V)

Reaction of diol **6** (for preparation, see U.S. Patent Number 4,152,527, which is

5   incorporated by this reference) with 3,4-dihydro-2H-pyran in CH_2Cl_2 at 0 °C in the

presence of TsOH affords THP ether **7**, which is reduced with diisobutylaluminum hydride

DIBAL-H in toluene at -78 °C to afford lactol **8**. Wittig reaction of **8** with

$Ph_3P^+CH_2OCH_3$ Cl⁻ in THF at 0 °C in the presence KOBu^t provides enol ether **9**, which is

hydrolyzed with TsOH in THF/water to yield lactol **10**. Wittig reaction of **10** with

10 $Ph_3P^+(CH_2)_3CO_2H$ Br⁻ in THF at 0 °C in the presence of KOBu^t, followed by alkylation of

the product carboxylic acid with isopropyl iodide in acetone in the presence of DBU,

yields **V** after purification *via* silica gel chromatography.

EXAMPLE 3:

Synthesis of VI
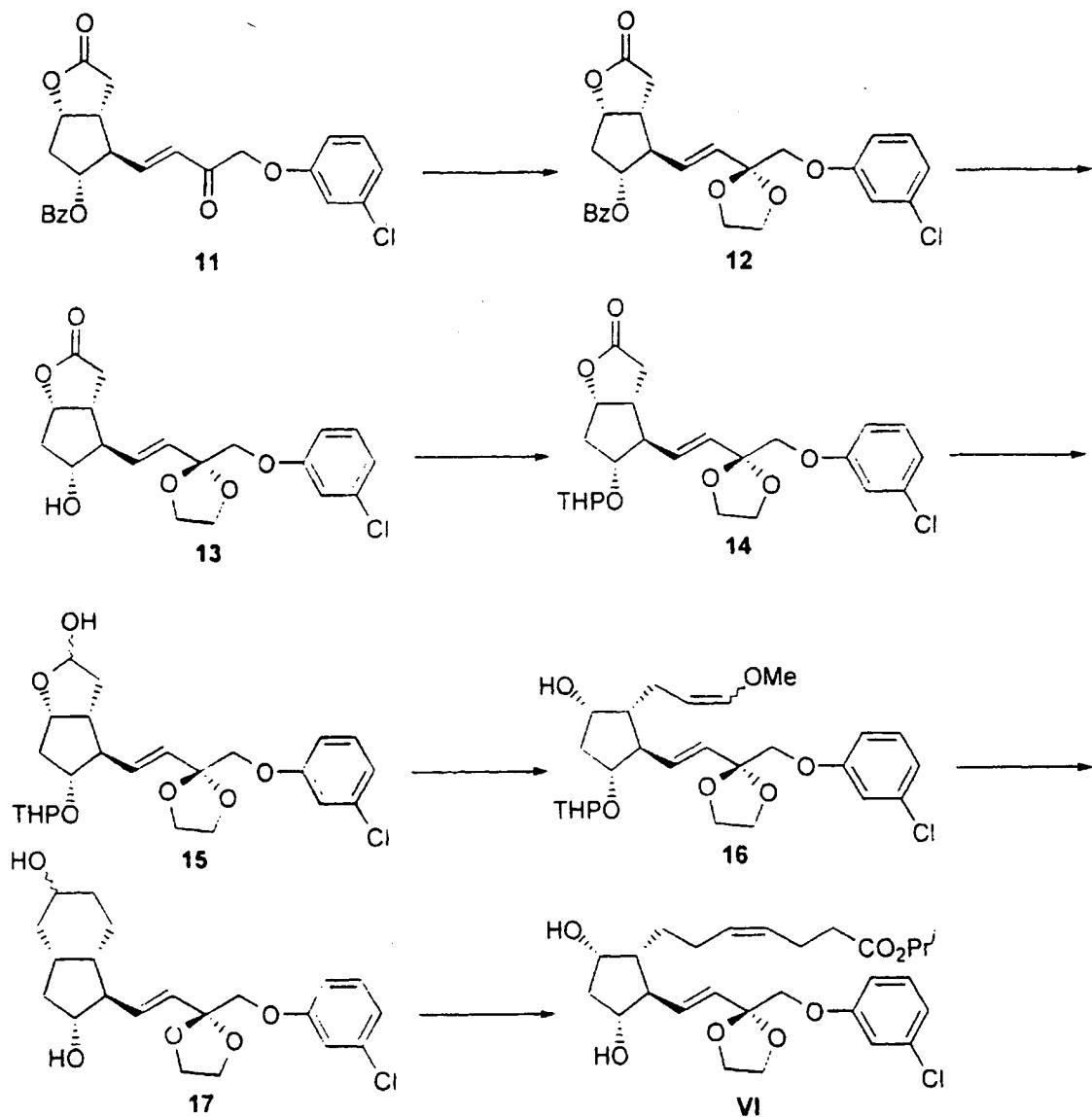
<u>(4Z,13E)-(9S,11R)-16-(3-Chlorophenoxy)-9,11-dihydroxy-15-(1,3-dioxolan-2-yl)-</u>
<u>17,18,19,20-tetranor-4,13-prostadienoic acid isopropyl ester (VI)</u>

Ketalization of enone **11** (for preparation, see published European Patent
Application No. EP 639563 A2, which is incorporated by this reference) with
$(Me_3SiOCH_2)_2$ in CH_2Cl_2 at -78 °C in the presence of $Me_3SiOSO_2CF_3$ affords ketal **12**,
which is debenzoylated with potassium carbonate in methanol to provide alcohol **13**.
Reaction of **13** with 3,4-dihydro-2*H*-pyran in CH_2Cl_2 at 0 °C in the presence TsOH affords
14, reduction of which with DIBAL-H in toluene at -78 °C provides lactol **15**. Wittig
reaction of lactol **15** with $Ph_3P^+CH_2OMe$ Cl⁻ in the the presence of KOBu^t in THF affords
enol ether **16** as a mixture of enol ether olefin geometrical isomers. Treatment of this
mixture with TsOH in THF/water affords lactol **17**. Wittig reaction of **17** with
$Ph_3P^+(CH_2)_3CO_2H$ Br⁻ in the presence of KOBu^t in THF, followed by treatment of an
acetone solution of the resulting carboxylic acid with DBU and isopropyl iodide, yields **VI**
after purification *via* silica gel chromatography.

EXAMPLE 4:

Synthesis of VII
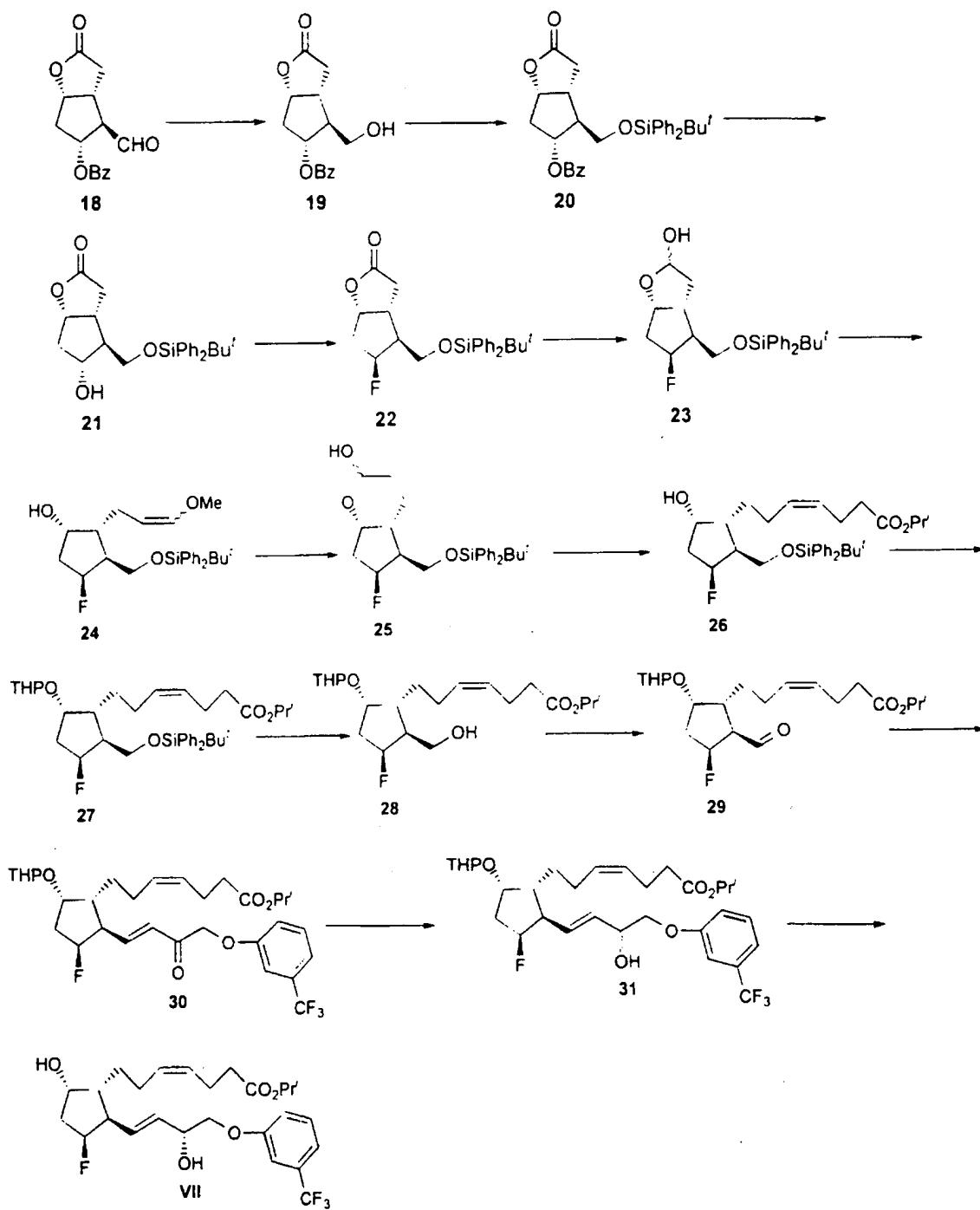
(4Z,13E)-(9S,11S,15R)-9,15-Dihydroxy-11-fluoro-16-[(3-trifluoromethyl)phenoxy]-17,18,19,20-tetranor-4,13-prostadienoic acid isopropyl ester (VII)

Reduction of aldehyde **18** with $NaBH_4$ in methanol/CH_2Cl_2 at 0 °C affords alcohol **19**, which is treated with Ph_2Bu^tSiCl in CH_2Cl_2 in the presence of imidazole and 4-(dimethylamino)pyridine to afford silyl ether **20**. Debenzoylation is effected using potassium carbonate in methanol to provide alcohol **21**, which is treated with (diethylamino)sulfur trifluoride (DAST) in CH_2Cl_2 at 0 °C. After work-up and purification of the reaction *via* silica gel chromatography, the residue is stirred overnight with catalytic OsO_4 in acetone in the presence of stoichiometric *N*-methylmorpholine *N*-oxide to provide fluoride **22** after purification *via* silica gel chromatography. Reduction of **22** with DIBAL-H affords lactol **23**, which is condensed with $Ph_3P^+CH_2OMe$ Cl^- in the the presence of $KOBu^t$ in THF to yield enol ether **24**. Acidic hydrolysis using TsOH in THF/water gives lactol **25**, which is reacted with $Ph_3P^+(CH_2)_3CO_2H$ Br^- in the presence of $KOBu^t$ in THF, followed by treatment of an acetone solution of the resulting carboxylic acid with DBU and isopropyl iodide, to afford alkene **26**. Treatment of **26** with 3,4-dihydro-2*H*-pyran in CH_2Cl_2 at 0 °C in the presence TsOH provides THP ether **27**, which is desilylated using tetra-*n*-butylammonium fluoride in THF to give alcohol **28**. Swern oxidation of **28** (oxalyl chloride, DMSO, CH_2Cl_2, NEt_3, -78 °C) affords aldehyde **29**, which is treated with $(MeO)_2P(O)CH_2C(O)CH_2OC_6H_4$-*m*-$CF_3$, NEt_3, and LiCl in THF to provide enone **30**. Luche reduction of **30** ($NaBH_4$, $CeCl_3$, MeOH, 0 °C) gives allyl alcohol **31** as a mixture of C-15 diastereomers. Acidic deprotection of **31** using aqueous HCl in isopropanol, followed by purification *via* silica gel chromatography, gives **VII**.

EXAMPLE 5:

Synthesis of VIII
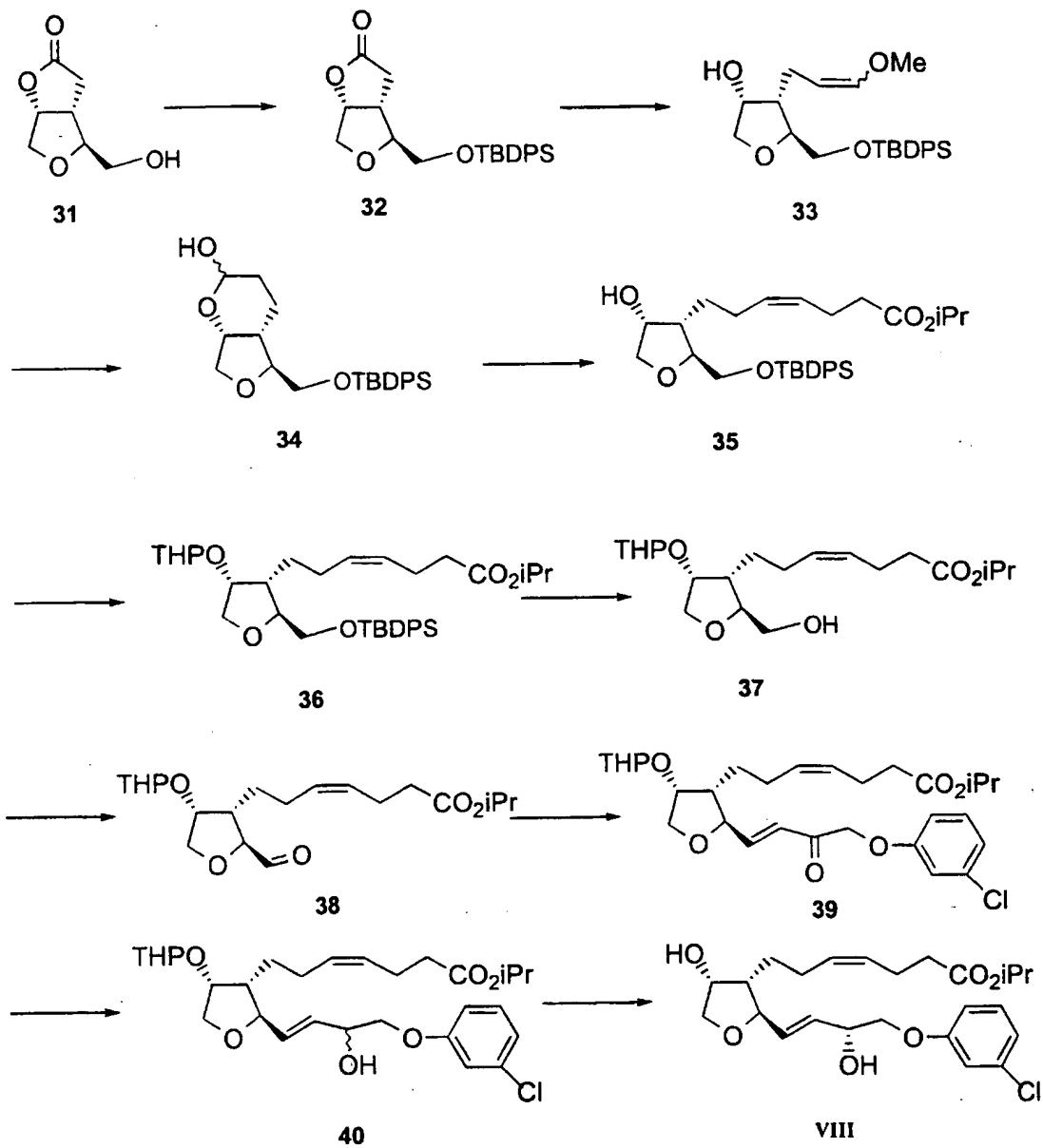
(3aR,4S,6aR)-4-(*tert*-Butyldiphenylsilyloxy)methylhexahydrofuro[3,4-b]furan-2-one (32)

A mixture of alcohol 31 (for preparation, see U.S. Patent No. 4,133,948, which is
incorporated by this reference) (5.0 g, 31.6 mmol) and imidazole (4.3 g, 63.2 mmol) was
5   dissolved in 100 mL of anhydrous DMF. To this solution *tert*-butyldiphenylsilyl chloride
(10.4 g, 38.0 mmol) was added and the resulting mixture was stirred at room temperature
for 14 h. The solvent was evaporated and the residue was taken up in 100 mL of EtOAc,
washed with water (2X50 mL), dilute aqueous solution of HCl (2X50 mL) and brine and
dried (MgSO4). The solvent was evaporated and the crude was purified by
10   chromatography on silica gel to afford 32 (12.4 g, quantitative yield) as a white solid: R_f
0.6 (60% EtOAc/hexanes). ^{1}H-NMR (CDCl$_3$) δ 7.65 (m, 4H), 7.42 (m, 6H), 5.10 (m, 1H),
4.25 (dd, J = 12, 4 Hz, 1H), 4.05 (dd, J = 12, 2 Hz, 1H), 3.85 (m, 1H), 3.75 (m, 2H), 3.00
(m, 1H), 2.82 (dd, J = 16, 7 Hz, 1H), 2.45 (dd, J = 16, 2 Hz, 1H), 1.05 (s, 9H).

15   Isopropyl [2S,3S(4Z),4R]-7-[Tetrahydro-2-(*tert*-butyldiphenylsilyloxy)methyl-4-hydroxy-
3-furanyl]-4-heptenoate (35)

A solution of the lactone 32 (5.7 g, 14.5 mmol) in 150 mL of anhydrous THF was
cooled to -78 °C under an inert atmosphere, and to it DIBAL-H (14.5 mL, 1.5 M in
20   toluene, 21.7 mmol) was added dropwise. The resulting mixture was stirred at -78 °C for
1.5 h and was then quenched at the same temperature by the addition of 5 mL of methanol.
The reaction was warmed to room temperature, an equal volume of a saturated aqueous
solution of potassium sodium tartrate was added to it, and the resulting slurry was stirred
at room temperature for 1 h. The layers were separated, and the aqueous layer was
25   extracted with 3X25 mL of EtOAc. The organic layers were combined and washed with
brine and dried (MgSO$_4$). The solution was filtered and concentrated and the crude was
purified by passage through a short column of silica gel to afford the intermediate lactol
(5.6 g, quantitative yield) as a colorless oil: R_f 0.5 (60% EtOAc/hexanes).

30   A suspension of (methoxymethyl)triphenylphosphonium chloride (2.5 g, 7.5
mmol) in 70 mL of dry THF was cooled to 0 °C under a N$_2$ atmosphere. To this solution

potassium *tert*-butoxide (*t*-BuOK, 9.0 mL, 1.0 M in THF, 9.0 mmol) was added dropwise,
and stirring was continued at 0 °C for an additional 20 min. At this time a solution of the
lactol obtained above (1.0 g, 2.5 mmol) in 30 mL of dry THF was added to it, and the
resulting mixture was stirred at 0 °C for 1.5 h. The reaction was then worked up by

5   pouring it into 50 mL of a saturated aqueous solution of KH_2PO_4, the layers were
separated and aqueous layer was extracted with 3X25 mL of EtOAc. The combined
organic layers were washed with water and brine, and dried ($MgSO_4$); solvent removal and
chromatography of the crude on silica afforded the enolether **33** (0.89 g, 83% yield) as a
colorless liquid: R_f 0.6 (60% EtOAc/hexanes).

10

A solution containing enolether **33** (2.45 g, 5.7 mmol), p-toluenesulfonic acid (0.1
g) and water (10 mL) in 150 mL of THF was heated at reflux for 3 h. The mixture was
then cooled to room temperature and poured into 50 mL of a saturated aqueous solution of
$NaHCO_3$. The layers were separated and aqueous layer was extracted with EtOAc. The

15   organic extracts were combined and dried ($MgSO_4$) and the crude product was subjected to
chromatography on silica to afford **34** (1.44 g, 60% yield) as a colorless liquid. This
material was used in the next reaction: R_f 0.28 (50% EtOAc/hexanes).

A suspension of (3-carboxypropyl)triphenylphosphonium bromide (4.5 g, 10.5

20   mmol) in 70 mL of dry THF was cooled to 0 °C and to it *t*-BuOK (21.0 mL, 1.0 M in
THF, 21.0 mmol) was added dropwise. The resulting solution was stirred for 30 min at 0
°C and to it a solution of the lactol **34** (1.44 g, 3.5 mmol) in 30 mL of dry THF was added
dropwise over a period of 10 min. The reaction was allowed to warm to room temperature
gradually, and was stirred at that temperature for 14 h. The mixture was then poured into

25   50 mL of a saturated aqueous solution of KH_2PO_4, and extracted with 3X25 mL of EtOAc.
The organic extracts were combined and washed with brine, and dried (MgSO4).
Filtration and solvent removal afforded an oily residue which was used immediately in the
subsequent step.

30   The crude product from above was dissolved in 40 mL of acetone and the solution
was treated with DBU (12.0 mL, 84 mmol) at room temperature for 10 min. Isopropyl

iodide (7.0 mL, 70 mmol) was then introduced and the resulting mixture was stirred at room temperature for 18 h. Solvent was evaporated, and the residue was dissolved in 50 mL of EtOAc. This solution was washed sequentially with 3X25 mL of a saturated aqueous solution of KH_2PO_4, 1X10 mL of water and brine and dried over anhydrous

MgSO$_4$. Filtration, solvent removal and chromatography of the crude on silica gel afforded the desired isopropyl ester **35** (1.18 g, 65% yield from **34**) as a slightly yellow liquid: R_f 0.2 (30% EtOAc/hexanes); ^{1}H-NMR (CDCl$_3$) δ 7.71 (m, 4H), 7.40 (m, 6H), 5.38 (m, 2H), 5.00 (septet, J = 6.4 Hz, 1H), 4.38 (m, 1H), 3.65-4.00 (broad m, 5H), 1.90-2.50 (broad m, 7H), 1.55 (m, 2H), 1.23 (d, J = 7.2 Hz, 6H), 1.05 (s, 9H); MS m/z at 547 for

(M+Na)$^+$.

Isopropyl [2S,3R(4Z),4R]-7-[Tetrahydro-2-hydroxymethyl-4-(tetrahydropyran-2-yl)oxy-3-furanyl]-4-heptenoate (37)

A solution of the alcohol **35** (1.18 g, 2.3 mmol) and 3,4-dihydro-2H-pyran (0.3 mL, 3.4 mmol) in 50 mL of CH$_2$Cl$_2$ was cooled to 0 °C and to it a catalytic amount of p-toluenesulfonic acid (10 mg) was added. The resulting mixture was stirred at 0 °C for 25 min and was then quenched by the addition of 25 mL of a saturated aqueous solution of NaHCO$_3$. The mixture was warmed to room temperature, the layers were separated and the aqueous layer was extracted with 3X25 mL of CH$_2$Cl$_2$. The organic layers were combined and washed with brine and dried (K$_2$CO$_3$). The crude obtained after filtration and solvent removal was purified by passage through a short plug of silica to afford the intermediate tetrahydropyranyl ether **36** as colorless liquid: R_f 0.4 (30% EtOAc/hexanes).

The silyl ether **36** thus obtained was dissolved in 20 mL of THF and the solution was treated with tetra-n-butylammonium fluoride (7.0 mL, 1.0 M in THF, 7.0 mmol) at room temperature for 2 h. The reaction mixture was then poured into water and was extracted with EtOAc (3X25 mL). The organic extracts were combined and dried (MgSO4), filtered and concentrated. The crude was subjected to chromatography on silica to afford the alcohol **37** (0.72 g, 85% yield from **35**) as a colorless liquid: R_f 0.16 (50%

EtOAc/hexanes); ^{1}H-NMR (d_6-DMSO) δ (partial spectrum) 5.36 (m, 2H), 4.87 (septet, J = 6.5 Hz, 1H), 4.60 (m, 2H), 1.18 (d, J = 7.2 Hz, 6H).

Isopropyl [2S,3R(4Z),4R]-7-[Tetrahydro-2-formyl-4-(tetrahydropyran-2-yl)oxy-3-furanyl]-4-heptenoate (38)

A solution of oxalyl chloride (2.0 mL, 2.0 M in CH_2Cl_2, 4.0 mmol) in 10 mL of dry CH_2Cl_2 was cooled to -78 °C, and to it a solution of DMSO (0.56 mL, 8.0 mmol) in 5 mL of CH_2Cl_2 was introduced dropwise. After the mixture was stirred for 3 min at -78 °C, a solution of the substrate 37 (0.72 g, 2.0 mmol) in 25 mL of CH_2Cl_2 was added to it dropwise. The mixture was stirred for 15 min, at which time triethylamine (1.7 mL, 12.0 mmol) was introduced, and stirring was continued for an additional 15 min. The reaction was gradually warmed to room temperature and then poured into 50 mL of water. The layers were separated and the water layer was extracted with 3X25 mL of CH_2Cl_2. The combined organic extracts were washed with water and brine, and dried ($MgSO_4$). Filtration and solvent removal, followed by chromatography of the crude on silica afforded the aldehyde 38 (0.69 g, 94% yield) as a pale yellow liquid: R_f 0.3 (50% EtOAc/hexanes); ^{1}H-NMR ($CDCl_3$) δ (partial spectrum) 9.66 (d, J = 3 Hz, 1H), 5.37 (m, 2H), 5.0 (septet, J = 6.5 Hz, 1H), 1.24 (d, J = 7.2 Hz, 6H).

Isopropyl [2R(1E),3R(4Z),4R]-7-[Tetrahydro-2-[4-(3-chlorophenoxy)-3-oxo-1-butenyl]-4-(tetrahydropyran-2-yl)oxy-3-furanyl]-4-heptenoate (39)

A mixture of the aldehyde 38 (0.32 g, 0.87 mmol), dimethyl-3-(3-chlorophenoxy)-2-oxopropylphosphonate (1.0 g, 3.5 mmol) and LiCl (0.15 g, 3.5 mmol) was taken up in 40 mL of dry THF, and the solution was cooled to 0 °C under a N_2 atmosphere. To this solution triethylamine (0.5 mL, 3.5 mmol) was added dropwise, and the resulting slurry was stirred at 0 °C for 1 h. The reaction was then quenched by pouring it into 50 mL of a saturated aqueous solution of KH_2PO_4. The organic layer was separated and the aqueous layer was extracted with 3X25 mL of EtOAc. The organic extracts were combined and washed with water and brine and dried ($MgSO_4$). The crude product mixture was

subjected to chromatography on silica to afford the enone **39** (0.34 g, 73% yield) as a pale yellow liquid: R_f 0.6 (60% EtOAc/hexanes); ^{1}H-NMR (CDCl$_3$) δ (partial spectrum) 6.70-7.20 (broad m, 5H), 6.12 (d, J = 16.7 Hz, 1H), 5.36 (m, 2H), 5.0 (septet, J = 6.5 Hz, 1H), 4.73 (s, 2H), 1.23 (d, J = 7.5 Hz, 6H).

5

Isopropyl [2R(1E,3RS),3R(4Z),4R]-7-[Tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-4-(tetrahydropyran-2-yl)oxy-3-furanyl]-4-heptenoate (**40**)

A mixture of the enone **39** (0.34 g, 0.64 mmol) and CeCl$_3$.7H$_2$O (0.47 g, 1.27
10 mmol) was dissolved in 30 mL of methanol and the solution was cooled to -5 °C. NaBH$_4$
(47 mg, 1.27 mmol) was added to the solution in small portions over a period of 3 min.
The mixture was stirred for an additional 3 min and the reaction was then quenched at -5
°C by the addition of 10 mL of a saturated aqueous solution of NH$_4$Cl. The resulting
slurry was warmed to room temperature and partitioned between CHCl$_3$ and water. The
15 aqueous layer was extracted with 3X25 mL of CHCl$_3$ and the combined organic extracts
were washed with 2X10 mL of water and brine. The organic layer was dried, filtered and
concentrated and the crude was purified by chromatography on silica to afford the
reduction product **40** (0.30 g, 87% yield) as a colorless liquid: R_f 0.24 (50%
EtOAc/hexanes).

20

Isopropyl [2R(1E,3R),3S(4Z),4R]-7-[Tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-4-hydroxy-3-furanyl]-4-heptenoate (**VIII**)

The allyl alcohol **40** (0.30 g, 0.55 mmol) was dissolved in a mixture of 10 mL of
25 methanol and 1.0 mL of water, and the solution was cooled to 0 °C. Approximately 10
drops of 12 N HCl was added to it dropwise, and stirring was continued at 0 °C for 15 min
and then at room temperature for 1 h. The reaction was then quenched by the addition of
solid NaHCO$_3$, and the suspension was partitioned between CHCl$_3$ and water. The layers
were separated and the aqueous layer was extracted with 3X25 mL of CHCl$_3$. The organic
30 extracts were combined and washed with water (2X10 mL) and brine and dried (Na$_2$SO$_4$).
Filtration and solvent removal gave an oil which was subjected to silica gel

chromatography to separate the two diastereomers. **VIII** (61 mg, 25% yield) was obtained as colorless liquid: R_f 0.15 (60% EtOAc/hexanes); ^{1}H-NMR (CDCl$_3$) δ 7.17 (m, 1H), 6.90 (m, 2H), 6.78 (m, 1H), 5.84 (m, 2H), 5.35 (m, 2H), 5.00 (septet, $J = 6.4$ Hz, 1H), 4.55 (m, 1H), 4.40 (m, 1H), 3.80-4.15 (broad m, 5H), 1.90-2.65 (broad m, 8H), 1.75 (m, 2H), 1.45 (m, 2H), 1.21 (d, $J = 7.4$ Hz, 6H); ^{13}C-NMR (CDCl$_3$) δ 173.08, 159.19, 134.90, 132.69, 130.68, 130.57, 130.26, 128.07, 121.35, 115.09, 113.04, 82.21, 75.45, 72.62, 71.83, 70.12, 67.94, 50.84, 34.36, 25.78, 24.55, 22.70, 21.89, 21.80; HRMS m/z calculated for C$_{24}$H$_{33}$O$_6$ClNa (M+Na$^+$) 475.185884, found 475.18588.

EXAMPLE 6:

Synthesis of IX
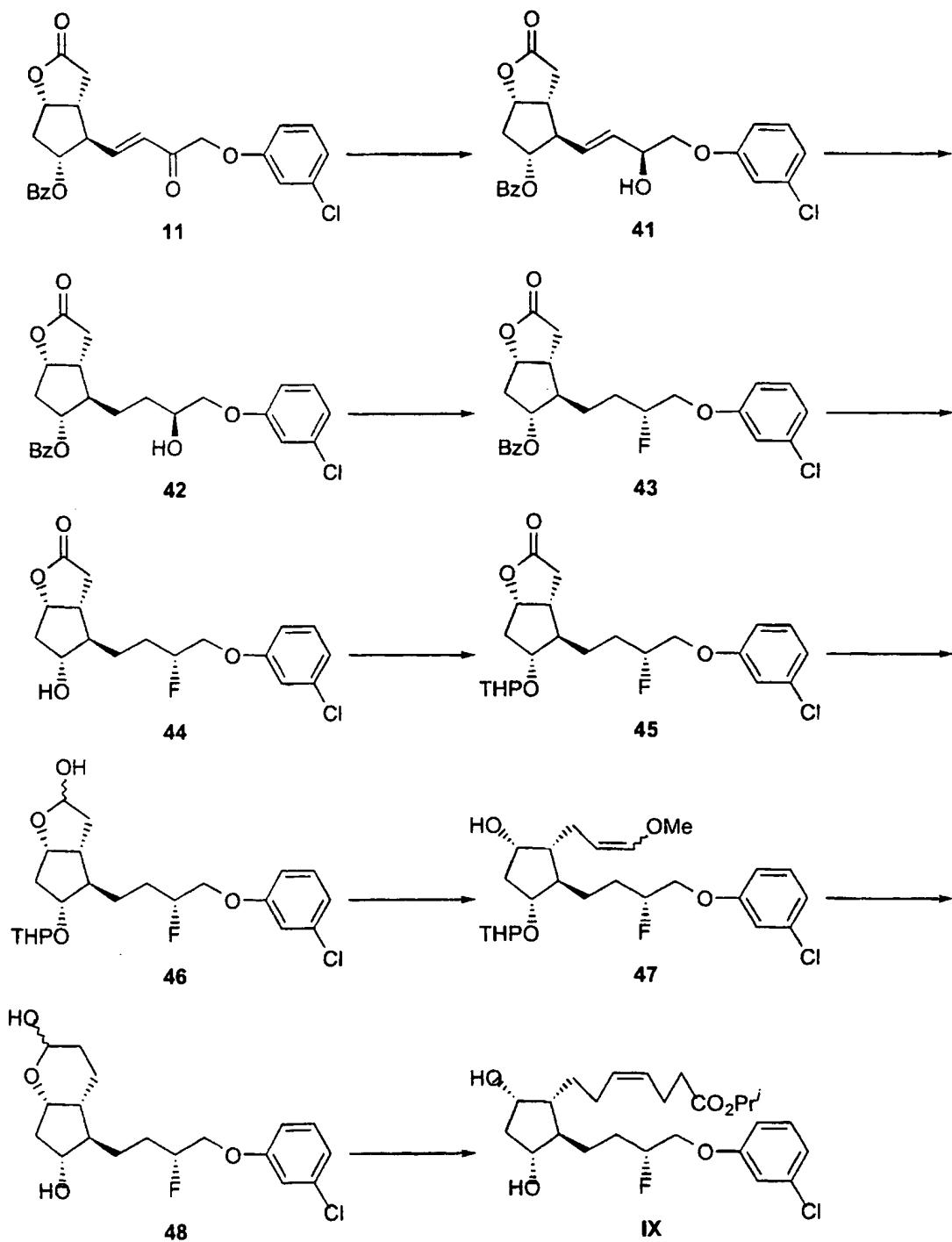
<u>(4Z)-(9S,11R,15R)-16-(3-Chlorophenoxy)-9,11-dihydroxy-15-fluoro-17,18,19,20-tetranor-4-prostenoic acid isopropyl ester (IX)</u>

Ketone reduction of 11 with (+)-*B*-chlorodiisopinocampheylborane in THF at 0 °C

5   affords C-15 β-hydroxy isomer **41** after chromatographic purification. Olefin reduction

using Pd/C under a hydrogen atmosphere in ethyl acetate solvent provides alcohol **42**,

which is fluorinated using DAST to yield α-fluoride **43**. Debenzoylation with potassium

carbonate in methanol gives alcohol **44**, which is treated with 3,4-dihydro-2*H*-pyran in

methylene chloride in the presence of TsOH to afford THP ether **45**. Reduction of **45** to

10   lactol **46** is effected with DIBAL-H at -78 °C in toluene, and Wittig condensation of **46**

with with $Ph_3P^+CH_2OMe$ Cl^- in the the presence of KOBu^t in THF yields enol ether **47**.

Acidic hydrolysis using TsOH in THF and water gives lactol **48**, which is reacted with

$Ph_3P^+(CH_2)_3CO_2H$ Br^- in the presence of KOBu^t in THF, followed by treatment of an

acetone solution of the resulting carboxylic acid with DBU and isopropyl iodide, to afford

15   **IX**.

The *cis*-Δ^4 analogs of the present invention may be formulated in various

pharmaceutical compositions for administering to humans and other mammals as a

treatment of glaucoma or ocular hypertension. As used herein, the term "pharmaceutically

20   effective amount" refers to that amount of a compound of the present invention which

lowers IOP when administered to a patient, especially a mammal. The preferred route of

administration is topical. The compounds of the present invention can be administered as

solutions, suspensions, or emulsions (dispersions) in an ophthalmically acceptable vehicle.

As used herein, the term "ophthalmically acceptable vehicle" refers to any substance or

25   combination of substances which are non-reactive with the compounds and suitable for

administration to a patient. Solubilizers and stabilizers are deemed to be non-reactive.

Preferred are aqueous vehicles suitable for topical application to the patient's eyes.

In forming compositions for topical administration, the compounds of the present

30   invention are generally formulated as between about 0.00003 to about 0.5 percent by

weight (wt%) solutions in water at a pH between 4.5 to 8.0. The compounds are

preferably formulated as between about 0.0005 to about 0.03 wt% and, most preferably, between about 0.001 and about 0.01 wt%. While the precise regimen is left to the discretion of the clinician, it is recommended that the resulting solution be topically applied by placing one drop in each eye one or two times a day.

Other ingredients which may be desirable to use in the ophthalmic preparations of the present invention include preservatives, co-solvents and viscosity building agents.

Antimicrobial Preservatives:

Ophthalmic products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, Onamer M, or other agents known to those skilled in the art. Such preservatives are typically employed at a level between about 0.001% and about 1.0% by weight.

Co-Solvents:

Prostaglandins, and particularly ester derivatives, typically have limited solubility in water and therefore may require a surfactant or other appropriate co-solvent in the composition. Such co-solvents include: Polysorbate 20, 60 and 80; Pluronic F-68, F-84 and P-103; CREMOPHORE® EL (polyoxyl 35 castor oil) cyclodextrin; or other agents known to those skilled in the art. Such co-solvents are typically employed at a level between about 0.01% and about 2% by weight.

<u>Viscosity Agents</u>:

Viscosity greater than that of simple aqueous solutions may be desirable to increase ocular absorption of the active compound, to decrease variability in dispensing the formulations, to decrease physical separation of components of a suspension or emulsion of formulation and/or otherwise to improve the ophthalmic formulation. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose, chondroitin sulfate and salts thereof, hyaluronic acid and salts thereof, and other agents known to those skilled in the art. Such agents are typically employed at a level between about 0.01% and about 2% by weight

Preferred formulations of cis-Δ^4 prostaglandins of the present invention include the following Examples 8-11:

EXAMPLE 8

Ingredient	Amount (wt%)
Compound **IV or V**	0.001
Phosphate Buffered Saline	1.0
Polysorbate 80	0.5
Purified water	q.s. to 100%

EXAMPLE 9

Ingredient	Amount (wt%)
Compound **IV** or **V**	0.001
Monobasic sodium phosphate	0.05
Dibasic sodium phosphate (anhydrous)	0.15
Sodium chloride	0.75
Disodium EDTA (Edetate disodium)	0.05
Cremophor EL	0.1
Benzalkonium chloride	0.01
HCl and/or NaOH	pH 7.3 - 7.4
Purified water	q.s. to 100%

EXAMPLE 10

Ingredient	Amount (wt%)
Compound IV or V	0.005
Monobasic sodium phosphate	0.05
Dibasic sodium phosphate (anhydrous)	0.15
Sodium chloride	0.75
Disodium EDTA (Edetate disodium)	0.05
CREMOPHOR® EL	0.1
Benzalkonium chloride	0.01
HCl and/or NaOH	pH 7.3 - 7.4
Purified water	q.s. to 100%

EXAMPLE 11

Ingredient	Amount (wt%)
Compound IV or V	0.01
Phosphate Buffered Saline	1.0
Hydroxypropyl-β-cyclodextrin	4.0
Purified water	q.s. to 100%

The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and

not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

What is claimed is:

1.   A method of treating glaucoma or ocular hypertension in a patient, which comprises administering to the patient a pharmaceutically effective amount of a compound of formula **III**:

III

wherein:

A = CO_2R, $CONR^1R^2$, CH_2OR^3, or $CH_2NR^4R^5$; where R = H or cationic salt moiety, or CO_2R = ophthalmically acceptable ester moiety; R^1, R^2 = same or different = H or alkyl; R^3 = H, acyl, or alkyl; R^4, R^5 = same or different = H, acyl, or alkyl, with the proviso that if one of R^4, R^5 = acyl, then the other = H or alkyl;

n = 0 or 2;

L = OR^6 in the α configuration, where R^6 = H, alkyl, or acyl;

B = R^7O , where R^7 = H, alkyl, acyl;

---- = single or *trans* double bond;

D, D^1 = different = H and OR^8, where R^8 = H, alkyl, acyl;

X = $(CH_2)_m$ or $(CH_2)_m O$, where m = 1-6; and

Y = a phenyl ring optionally substituted with alkyl, halo, trihalomethyl, alkoxy, acyl, acyloxy, amino, alkylamino, acylamino, or hydroxy; or

X-Y = $(CH_2)_p Y^1$; where p = 0-6; and

wherein:

W = CH_2, O, $S(O)_q$, NR^9, CH_2CH_2, CH=CH, CH_2O, $CH_2S(O)_q$, CH=N, or CH_2NR^9; where q = 0-2, and R^9 = H, alkyl, or acyl;

Z = H, alkyl, alkoxy, acyl, acyloxy, halo, trihalomethyl, amino, alkylamino, acylamino, or hydroxy; and

---- = single or double bond;

with the proviso that if:
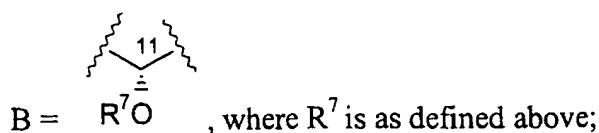
L = OR^6 in the α configuration, where R^6 is as defined above;

B = R^7O , where R^7 is as defined above;

--- = trans double bond;

D, D^1 = different = H and OR^8, where R^8 is as defined above; and

X = CH_2CH_2 or CH_2O; then

Y ≠ a phenyl ring, optionally substituted with halo.

2.   The method of claim 1, wherein the compound is administered topically.

3.   The method of claim 2, wherein the compound is administered as a solution, suspension or emulsion.

4.   The method of claim 1, wherein:

A = CO_2R, where R = H; or CO_2R = ophthalmically acceptable ester moiety, where R = alkyl;

n = 0;

L = OH in the α configuration;

R^6 = H;
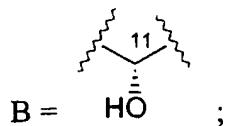
B =   ;

D = OH in the α configuration, and D^1 = H in the β configuration;

X = CH_2CH_2 or CH_2O; and

Y = phenyl, optionally substituted with halo or trihalomethyl; or

X-Y =

   ;

with the proviso that if:

L = OH in the α configuration;

$$B = \overset{\overset{\text{11}}{\underset{\text{HO}}{\Large\wedge\wedge}}}{\quad} \quad ;$$
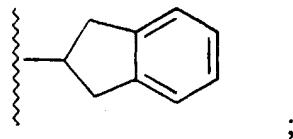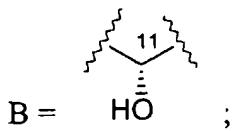
--- = *trans* double bond;

D = OH in the α configuration, and D^1 = H in the β configuration; and

X = CH_2CH_2 or CH_2O; then

Y ≠ a phenyl ring, optionally substituted with halo.

5. The method of claim 2, wherein the concentration of the compound is between about 0.00003 to about 0.5 weight percent.

6. The method of claim 5, wherein the concentration of the compound is between about 0.0005 to about 0.03 weight percent.

7. The method of claim 6, wherein the concentration of the compound is between about 0.001 to about 0.01 weight percent.

8. The method of claim 5, wherein the compound is:
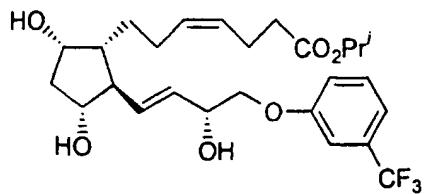
9.   The method of claim 5, wherein the compound is:
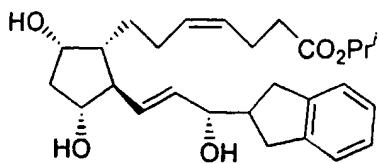
10.   A compound of formula **III**:

III
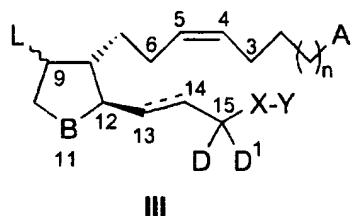
wherein:

A = CO_2R, $CONR^1R^2$, CH_2OR^3, or $CH_2NR^4R^5$; where R = H or a cationic salt moiety or CO_2R forms a pharmaceutically acceptable ester moiety; R^1, R^2 = same or different = H or alkyl; R^3 = H, acyl, or alkyl; R^4, R^5 = same or different = H, acyl, or alkyl; with the proviso that if one of R^4, R^5 = acyl, then the other = H or alkyl;

n = 0 or 2;

L = OR^6 in the α configuration, where R^6 = H, alkyl, or acyl;
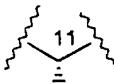
B = R^7O , where R^7 = H, alkyl, acyl;

---- = single or *trans* double bond;

D, D^1 = different = H and OR^8, where R^8 = H, alkyl, acyl;

X-Y = (CH$_2$)$_p$Y^1; where p = 0-6; and
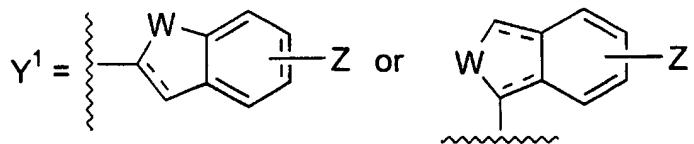
wherein:

W = CH$_2$, O, S(O)$_q$, NR^9, CH$_2$CH$_2$, CH=CH, CH$_2$O, CH$_2$S(O)$_q$, CH=N, or CH$_2$NR^9; where q = 0-2, and R^9 = H, alkyl, or acyl;

Z = H, alkyl, alkoxy, acyl, acyloxy, halo, trihalomethyl, amino, alkylamino, acylamino, or hydroxy; and

---- = single or double bond.

11.   The compound of claim 10, wherein:

A = CO_2R, where R = H; or CO_2R = pharmaceutically acceptable ester moiety, where R = or alkyl;

n = 0;

L = OH in the α configuration;

B =
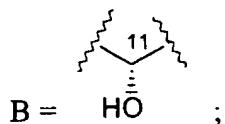
D = OH in the α configuration, and D^1 = H in the β configuration;

X-Y =
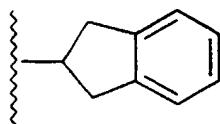
12.   The compound of claim 11, having the formula:
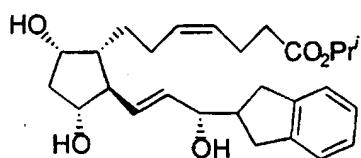
13.   A topical ophthalmic composition for the treatment of glaucoma and ocular hypertension, comprising a compound of formula **III**:


III

wherein:

A = CO_2R, $CONR^1R^2$, CH_2OR^3, or $CH_2NR^4R^5$; where R = H or cationic salt moiety, or CO_2R = ophthalmically acceptable ester moiety; R^1, R^2 = same or different = H or alkyl; R^3 = H, acyl, or alkyl; R^4, R^5 = same or different = H, acyl, or alkyl, with the proviso that if one of R^4, R^5 = acyl, then the other = H or alkyl;

n = 0 or 2;

L = OR^6 in the α configuration, where R^6 = H, alkyl, or acyl;


B = R^7O , where R^7 = H, alkyl, acyl;

---- = single or *trans* double bond;

D, D^1 = different = H and OR^8, where R^8 = H, alkyl, acyl;

X = $(CH_2)_m$ or $(CH_2)_mO$, where m = 1-6; and

Y = a phenyl ring optionally substituted with alkyl, halo, trihalomethyl, alkoxy, acyl, acyloxy, amino, alkylamino, acylamino, or hydroxy; or

X-Y = $(CH_2)_p Y^1$; where p = 0-6; and

wherein:

W = CH_2, O. $S(O)_q$, NR^9, CH_2CH_2, CH=CH, CH_2O, $CH_2S(O)_q$, CH=N, or CH_2NR^9; where q = 0-2, and R^9 = H, alkyl, or acyl;

Z = H, alkyl, alkoxy, acyl, acyloxy, halo, trihalomethyl, amino, alkylamino, acylamino, or hydroxy; and

---- = single or double bond;

and an ophthalmically acceptable vehicle therefor;

with the proviso that if:
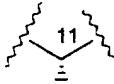
L = OR^6 in the α configuration, where R^6 is as defined above;

B = R^7O , where R^7 is as defined above;

--- = *trans* double bond;

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D, D^1 = different = H and OR^8, where R^8 is as defined above; and

X = CH_2CH_2 or CH_2O; then

Y ≠ a phenyl ring, optionally substituted with halo.

14. The composition of claim 13, wherein:

A = CO_2R, where R = H; or CO_2R = ophthalmically acceptable ester moiety, where R = or alkyl;

n = 0;

L = OH in the α configuration;

B =

D = OH in the α configuration, and D^1 = H in the β configuration;

X = CH_2CH_2 or CH_2O; and

Y = phenyl, optionally substituted with halo or trihalomethyl; or

X-Y =

;

with the proviso that if:

L = OH in the α configuration;

B =   HO⁻   ;
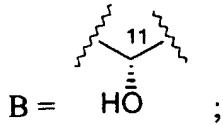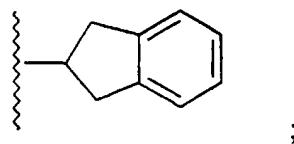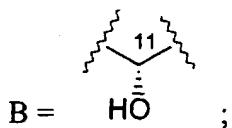
--- = *trans* double bond;

D = OH in the α configuration, and D^1 = H in the β configuration; and

X = CH$_2$CH$_2$ or CH$_2$O; then

Y ≠ a phenyl ring, optionally substituted with halo.

15.   The composition of claim 14, wherein the compound is:

16.   The composition of claim 14, wherein the compound is: